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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/725,652	11/29/2000	Eric Steven Furfine	PU3761US2	9583

23347 7590 01/24/2005

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EXAMINER	
CALAMITA, HEATHER	
ART UNIT	**PAPER NUMBER**
1637	

DATE MAILED: 01/24/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/725,652	FURFINE ET AL.	
	Examiner	Art Unit	
	Heather G. Calamita, Ph.D.	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-54* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

1. This action is in response to Applicants' response, filed on December 7, 2004. Currently, claims 1-54 are pending and are rejected. This action is made NON-FINAL. Any objections and rejections not reiterated below are hereby withdrawn.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-6, 11-23, 28-41, 46-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Haugland et al. (USPN 6,399,392 B1 06/04/2002) in view of Wittwer et al. (USPN 6,174,670 B1, 01/16/2001).

Haugland et al. teach a method of detecting polynucleic acid polymerase activity, the method comprising:

(b) mixing the polynucleic acid primer-template complex and the nucleotide with a sample comprising or suspected to comprise a polynucleic acid polymerase;

(c) prior to, contemporaneously with or after the mixing of step (b), exposing the labeled polynucleic acid primer-template complex and the labeled nucleotide to radiation of excitation wavelength for one of the energy-emitting chemical species to thereby excite that energy-emitting chemical species; and

(d) detecting a signal produced by energy transfer between the excited energy-emitting chemical species and the other energy-emitting chemical species as a result of incorporation of the nucleotide into the polynucleic acid primer-template complex via the activity of the polynucleic acid polymerase, the detection of the signal indicating polynucleic acid polymerase activity in the sample (see col. 50 lines 14-26).

With regard to claim 2, Haugland et al. teach the nucleotide is selected from the group consisting of dUTP, dTTP, dATP, dCTP, dGTP, ATP, CTP, UTP, GTP and combinations thereof (see col. 49 lines 61-63, col. 50 lines 18-19). With regard to claim 3, Haugland et al. teach the energy-emitting chemical species on the polynucleic acid primer-template complex is a donor chemical species and the energy-emitting chemical species on the nucleotide is an acceptor chemical species or wherein the energy-emitting chemical species on the nucleotide is a donor chemical species and the energy-emitting chemical species on the polynucleic acid primer-template complex is an acceptor chemical species(see col. 49 lines 44-65). With regard to claim 4, Haugland et al. teach the energy-emitting chemical species on the polynucleic acid primer-template complex and the energy-emitting chemical species on the nucleotide are light-emitting chemical species (see col. 49 lines 44-65). With regard to claim 5, Haugland et al. teach the light-emitting chemical species are each selected from the group consisting of a fluorescent compound, a phosphorescent compound, a chemiluminescent compound, and a bioluminescent compound (see col. 49 line 44-65). With regard to claim 6, Haugland et al. teach the fluorescent compound is selected from the group consisting of fluorescein and derivatives thereof, rhodamine and derivatives thereof, phycoerythrin, phycocyanin, allophycocyanin, o-phthaldehyde, fluorescamine, Texas red, cascade blue, Oregon green, phycoerythrin, CY3, CY5, CY2, CY7, coumarin, infrared 40, MR 200 and IRD 40 (see col. 49 lines 44-65). With regard to claim 13, Haugland et al. teach the polynucleic acid polymerase is a DNA polymerase or a RNA polymerase (see col. 49 line 53). With regard to claim 14, Haugland et al. teach the polymerase is a reverse transcriptase (see col. 49 line

66). With regard to claim 14, Haugland et al. teach further comprising detecting the signal at a plurality of time points over a predetermined time-period (see col. 49 line 63). With regard to claim 16, Haugland et al. teach further comprising screening a plurality of samples simultaneously for polynucleic acid polymerase activity (see col. 50 lines 8-11). With regard to claim 17, Haugland et al. teach the steps (a) through (d) are carried out for each sample in a single well of a multi-well plate (see col. 49 line 64). With regard to claims 18 and 37, Haugland et al. teach identifying a candidate compound as a modulator of polynucleic acid polymerase activity, the method comprising:

(a) providing a candidate compound, a polynucleic acid primer-template complex labeled with an energy-emitting chemical species and a nucleotide labeled with an energy-emitting chemical species,

(b) mixing the candidate compound, the polynucleic acid primer-template complex and the nucleotide with a polynucleic acid polymerase,

(c) prior to, contemporaneously with or after the mixing of step (b), exposing the labeled polynucleic acid primer-template complex and the labeled nucleotide to radiation of excitation wavelength for one of the energy-emitting chemical species to thereby excite that energy-emitting chemical species,

(d) detecting a signal produced by energy transfer between the excited energy-emitting chemical species and the other energy-emitting chemical species as a result of incorporation of the nucleotide into the polynucleic acid primer-template complex via the activity of the polynucleic acid polymerase, the detected signal indicating an amount of polynucleic acid polymerase activity and

(e) identifying the candidate compound as a modulator of polynucleic acid polymerase activity based on the amount of signal detected as compared to a control sample (see col. 50 lines 13-25). With regard to claims 19 and 38, Haugland et al. teach the nucleotide is selected from

the group consisting of dUTP, dTTP, dATP, dCTP, dGTP, ATP, CTP, UTP, GTP and combinations thereof (see col. 49 lines 61-63, col. 50 lines 18-19). With regard to claims 20 and 39, Haugland et al. teach the energy-emitting chemical species on the polynucleic acid primer-template complex is a donor chemical species and the energy-emitting chemical species on the nucleotide is an acceptor chemical species or wherein the energy-emitting chemical species on the nucleotide is a donor chemical species and the energy-emitting chemical species on the polynucleic acid primer-template complex is an acceptor chemical species (see col. 49 lines 44-65). With regard to claim 21, Haugland et al. teach the energy-emitting chemical species on the polynucleic acid primer-template complex and the energy-emitting chemical species on the nucleotide are light-emitting chemical species (see col. 49 lines 44-65). With regard to claims 22 and 40, Haugland et al. teach the light-emitting chemical species are each selected from the group consisting of a fluorescent compound, a phosphorescent compound, a chemiluminescent compound, and a bioluminescent compound (see col. 49 lines 44-65). With regard to claims 23 and 41, Haugland et al. teach the fluorescent compound is selected from the group consisting of fluorescein and derivatives thereof, rhodamine and derivatives thereof, phycoerythrin phycocyanin, allophycocyanin, o-phthaldehyde, fluorescamine, Texas red, cascade blue, Oregon green, phycoerythrin, CY3, CY5, CY2, CY7, coumarin, infrared 40, MR 200 and IRD 40 (see col. 49 lines 44-65). With regard to claims 30 and 49 Haugland et al. teach the polynucleic acid polymerase is a DNA polymerase or a RNA polymerase (see col. 49 line 53). With regard to claims 31 and 50, Haugland et al. teach the polymerase is a reverse transcriptase (see col. 49 line 66). With regard to claim 32, Haugland et al. teach further comprising detecting the signal at a plurality of time points over a predetermined time period (see col. 49 line 63). With regard to claims 35, Haugland et al. teach further comprising screening a plurality of candidate compounds simultaneously for polynucleic acid polymerase modulator activity (see col. 49 lines 53-56). With regard to claims 36, Haugland et al. teach steps (a) through (d) are carried out for each sample in a single well of a multi-well plate (see col. 49 line 64). With regard to claims 53, Haugland et al. teach

further comprising screening a plurality of candidate compounds simultaneously for polynucleic acid polymerase modulator activity (see col. 49 lines 53-56). With regard to claims 54, Haugland et al. teach steps (a) through (d) are carried out for each sample in a single well of a multi-well plate (see col. 49 line 64).

Haugland et al. do not teach (a) providing a polynucleic acid primer-template complex labeled with an energy-emitting chemical species and a nucleotide labeled with an energy-emitting chemical species.

Wittwer et al. do teach a polynucleic acid primer-template complex labeled with an energy-emitting chemical species and a nucleotide labeled with an energy-emitting chemical species (see col. 6 lines 38-42).

One of ordinary skill in the art at the time the invention was made would have been motivated to apply the polynucleic acid primer-template as taught by Wittwer et al. to the method for measuring enzyme activity with FRET as taught by Haugland et al. in order to produce a light-emitting primer-template complex for use in the energy transfer assay. Wittwer et al. state, "fluorimetry is a sensitive and versatile technique with many applications in molecular biology (see col. 2 lines 14-15)." Wittwer et al. further says "Fluorescent probes can be used to detect and monitor DNA amplification (see col. 21 lines40-41)." It would have been prima facie obvious to apply the polynucleic acid primer-template as taught by Wittwer et al. to the method for measuring enzyme activity with FRET as taught by Haugland et al. in order to achieve the expected advantage of a resonance energy transfer pair (the label on the primer-template complex and the label on the nucleotide) to assess the activity of the polymerase.light-emitting compound for use in the FRET assay.

3.Claims 7-10, 24-27, 42-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Haugland et al. (USPN 6,399,392 B1 06/04/2002) and Wittwer et al. (USPN 6,174,670 B1, 01/16/2001) in view of Bell et al. (USPN 5,4,35,937, 07/25/1995)

The combined teachings of Haugland et al. and Witter et al. are described previously.

Haugland et al. and Wittwer et al. do not teach (claims 7, 24, 42) the light-emitting chemical species on the polynucleic acid primer-template complex the light-emitting chemical species on the nucleotide or both the light-emitting chemical species on the polynucleic acid primer-template complex and the light-emitting on the nucleotide are rare earth metals. With regard to claims 8, 25, 43, Haugland et al. and Wittwer et al. do not teach the rare earth metal light- emitting chemical species on the polynucleic acid primer-template complex, the rare earth metal light-emitting chemical species on the nucleotide or both the rare earth metal light-emitting chemical species on the polynucleic acid primer-template complex and the rare earth metal light-emitting chemical species on the nucleotide are lanthanides. With regard to claims 9, 26, 44, Haugland et al. and Wittwer et al. do not teach the lanthanide further comprises a lanthanide chelate. With regard to claim 10, 27, 45, Haugland et al. and Wittwer et al. do not teach the lanthanide chelate further comprises lanthanum, cerium, praseodymium, neodymium, promethium, samarium, europium, gadolinium, terbium, dysprosium, holmium, erbium, thulium, ytterbium or lutetium.

Bell et al. teaches light-emitting chemical species are rare earth metals (see col. 1 lines 4-6). With regard to claim 8, teach the rare earth metal light-emitting chemical species are lanthanides (see col. 1 lines 4-6). With regard to claim 9, teach the lanthanide further comprises a lanthanide chelate (see col. 1 lines 4-6). With regard to claim 10, teach the lanthanide chelate further comprises lanthanum, cerium, praseodymium, neodymium, promethium, samarium, europium, gadolinium, terbium, dysprosium, holmium, erbium, thulium, ytterbium or lutetium (see col. 10 example 4).

One of ordinary skill in the art at the time the invention was made would have been motivated to apply Bell's lanthanide and lanthanide chelate to the teachings of Haugland and Wittwer for measuring enzyme activity with FRET in order to produce a light-emitting compound for use in the FRET assay. Bell et al. state, "polymer bodies which are light-emitting by virtue of containing a lanthanide or actimide chelate" (see col. 1 lines 4-6). It would have been prima facie obvious to apply Bell's lanthanide chelate with the method of Haugland and Wittwer for measuring enzyme activity with FRET in order to achieve the expected advantage of a light-emitting compound for use in the FRET assay.

4. Claims 11, 12, 28, 29, 46, 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Haugland et al. (USPN 6,399,392 B1 06/04/2002) and Wittwer et al. (USPN 6,174,670 B1, 01/16/2001) in view of Massey et al. (USPN 5,770,459 06/23/1998).

The combined teachings of Haugland et al. and Witter et al. are described previously.

Haugland et al. and Wittwer et al. do not teach (claims 11, 28, 46) teach the chemiluminescent compound is selected from the group consisting of luminol, isoluminol, theromatic acridinium ester and acridinium salt. With regard to claims 12, 29, 47, Haugland et al. and Wittwer et al. do not teach the bioluminescent compound is selected from the group consisting of luciferin, luciferase and aequorin.

Massey et al. teach the chemiluminescent compound is selected from the group consisting of luminol, isoluminol, theromatic acridinium ester and acridinium salt (see col. 5 lines 15-18). Massey et al. teach the bioluminescent compound is selected from the group consisting of luciferin, luciferase and aequorin (see col. 5 lines 15-18).

One of ordinary skill in the art at the time the invention was made would have been motivated to apply Massey's method of use for chemiluminescent compounds with the teachings of Haugland and Wittwer for measuring enzyme activity with FRET in order to determine the point at which enzyme activity was inhibited by the binding of a compound. Massy et al. state, "Chemiluminescent labels which

have been used in specific binding assays include..." (see col. 5 lines 15-16). It would have been prima facie obvious to apply Massey's method of use for chemiluminescent compound with the teachings of Haugland and Wittwer for measuring enzyme activity with FRET to achieve the expected advantage of detecting the point at which enzyme activity was inhibited by the binding of a compound.

5. Claims 33 and 51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Haugland et al. (USPN 6,399,392 B1 06/04/2002) Wittwer et al. (USPN 6,174,670 B1, 01/16/2001) in view of Cunningham et al. (5,534,617 07/09/1996).

The combined teachings of Haugland et al. and Witter et al. are described previously.

Haugland et al. and Wittwer et al. do not teach (claims 33 and 51) calculating an association constant and dissociation constant for the candidate compound for modulation of polynucleic acid polymerase activity.

Cunningham et al. teach calculating an association constant and dissociation constant (see col. 24 lines 44-46).

One of ordinary skill in the art at the time the invention was made would have been motivated to apply Cunningham's calculation of an association/dissociation constant with the teachings of Haugland and Wittwer for measuring enzyme activity with FRET in order to determine association rates of the enzyme. It would have been prima facie obvious to apply Cunningham's calculation of an association/dissociation constant with the teachings of Haugland and Wittwer for measuring enzyme activity with FRET to achieve the expected advantage of determining the avidity with which an enzyme binds its substrate.

6. Claims 34 and 52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Haugland et al. (USPN 6,399,392 B1 06/04/2002) Wittwer et al. (USPN 6,174,670 B1, 01/16/2001) in view of Hill et al. (5,726,195 03/10/1998).

The combined teachings of Haugland et al. and Witter et al. are described previously.

Haugland et al. and Wittwer et al. do not teach (claim 34 and 52) calculating an IC_{50} value for the candidate compound for modulation of polynucleic acid polymerase activity.

Hill teaches calculating an IC_{50} value (see col. 35 lines 1-7).

One of ordinary skill in the art at the time the invention was made would have been motivated to apply Hill's calculation of an IC_{50} value with the teachings of Haugland and Wittwer for measuring enzyme activity with FRET in order to the inhibitory concentration of a substance that inhibits enzyme activity. It would have been prima facie obvious to apply Hill's calculation of an IC_{50} value with the teachings of Haugland and Wittwer for measuring enzyme activity with FRET to achieve the expected advantage of determining the concentration at which enzyme activity was inhibited upon addition of a test compound.

Summary

7. No claims were allowed.

Conclusion

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Heather G. Calamita, Ph.D. whose telephone number is 571.272.2876 and whose e-mail address is heather.calamita@uspto.gov. However, the office cannot guarantee security through the e-mail system nor should official papers be transmitted through this route. The examiner can normally be reached on Monday thru Thursday 7:00 A.M. - 5:30 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571.272.0782. The fax phone number for the organization where this application or proceeding is assigned is 571.273.8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

hgc

KENNETH R. HORLICK, PH.D
PRIMARY EXAMINER

1/12/05